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PATENT APPLICATION

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Stephen A. Slusher, Reg. No. 43,924

August 3, 2001  
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: GEORGE R. SCHWARTZ

Examiner: Chih-Min Kam

Serial No. 09/642,236

Group Art Unit: 1653

Filed: August 17, 2000

For: INDUCED REGENERATION AND REPAIR  
OF DAMAGED NEURONS AND NERVE  
AXION MYELIN

DECLARATION OF GEORGE R. SCHWARTZ UNDER 37 C.F.R. § 1.68

Commissioner for Patents  
Washington, D.C. 20231

Sir:

George R. Schwartz declares as follows:

1. I am the inventor of the subject matter of the above-identified patent application.
2. I am a medical doctor, and a copy of my curriculum vitae is attached to this declaration as

Attachment A.

3. It is known in the art that administration of thrombopoietin results in the production of platelets. Thrombopoietin is prescribed and used for thrombocytopenia, a condition commonly defined as a platelet count below about  $150 \times 10^9$  per liter. There are many causes of thrombocytopenia, including impaired production of platelets by the blood marrow, such as results from radiation therapy or

chemotherapy, autoimmune disorders resulting in destruction of platelets in the peripheral circulation, and platelet sequestration in the spleen. For these disease conditions, the utility of thrombopoietin in increasing production of platelets, and doses of administration to effect increased platelet production, are generally taught in U.S. Patent Nos. 5,795,569; 5,879,673; and 5,989,537. Each of the foregoing U.S. patents is disclosed in the above-identified patent application, and is incorporated by reference therein. It is also known in the art that administration of thrombopoietin will cause increases in platelet counts even in the absence of any form of thrombocytopenia. Thus thrombopoietin has been used to increase platelet counts prior to administration of a therapy, such as chemotherapy, which will result in inducing thrombocytopenia. See, for example, Vadhan-Ray, *Seminars in Hematology*, 35:261-268 (1998) (included in the Information Disclosure Statement filed with this application).

4. It is known in the art that production of endogenous platelet derived growth factor is increased upon administration of thrombopoietin. While platelet derived growth factor is produced by several types of cells in the human body, the largest and primary source of platelet derived growth factor is from platelets.

5. With respect to the animal experiments of Examples 1 to 3, it is known from Chiu AY et al.: Age-dependent penetrance of disease in a transgenic mouse model of familial amyotrophic lateral sclerosis. *Mol Cell Neurosci* 6:349-362 (1995), that the onset of clinical disease in the specific animal model employed is at  $91 \pm 14$  days of age. This paper is cited in the patent application at page 10, lines 22-24, and a copy is attached to this declaration as Attachment B. As the Examiner notes in the Office Action, the data in the Examples "indicate a delay on the symptoms of illness in the transgenic mouse model." It is true that there is no "placebo group" as such, but given the design of the studies, and the state of knowledge with respect to this specific animal model, no control group is required. The time course of illness and death is well established in the specific animal model used. Further, it is known and well established that the disease expression in this animal model is progressive and without spontaneous improvement unless an effective therapy is initiated. It should also be observed that in the design of the experiment the mouse of each described Example serves as a control for one or more other

Examples. Thus in Example 1, mouse A began manifesting objective symptoms of limb paralysis at day 105 following birth. Page 10, lines 26-27. Mouse B of Example 2 was a litter mate of Mouse A (page 11, lines 15-16). It is known and accepted that litter mates in a model such as this will generally have a similar time to onset of objective symptoms and disease progression. The treatment protocol for mouse B of Example 2 was initiated prior to the onset of objective symptoms, and no objective symptoms were observed until day 121. Page 12, lines 2-4. As noted in Example 2, this was 16 days later than the onset of objective symptoms with Mouse A of Example 2. Thus Mouse A, which received no treatment prior to onset of symptoms, served as a control with respect to onset of symptoms for Mouse B.

6. The animal studies were conducted to confirm, in part, the hypothesis that administration of thrombopoietin and a regulatory agent such as thyroid hormone or thyrotropin would be efficacious in treatment of neurologic damage. The end point of such treatment is, in the context of this patent application, either a delay in the onset of objective symptoms in a progressive disease, or an increase in neurological function following the onset of symptoms. Both end points are illustrated in the described animal data of Examples 1 to 3. The hypothesis is based in part upon prior scientific data that predicted that growth factors, such as platelet derived growth factors, could be used as a potential therapy for central nervous system demyelination disorders, see, for example, J. B. Grinspan et al: *Annals of Neurology* 36:5140-5142 (Suppl) (1994) and C. Fressinaud: *GLIA* 16:40-50 (1996) (both contained in Information Disclosure Statement). Prior art further predicted that thyroid hormone or thyrotropin contributes to remyelination of oligodendrocytes, though it is not sufficiently efficacious to be used solely by itself. See, e.g., R. J. M. Franklin and J. M. Gilson: *NeuroReport* 7:1526-1530 (1996) and M. E. Brooke: *Ann NY Acad Sci* 553:422-430 (1989) (both contained in Information Disclosure Statement).

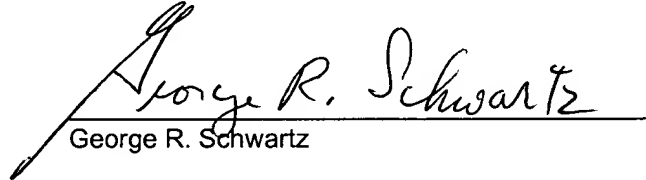
7. The sites of administration of each of thrombopoietin, thyroid hormone and thyrotropin are well known in the art. The invention does not rely upon use of any specific site of administration, so long as the site of administration is efficacious in terms of delivering the drug. For example, U.S. Patent Nos. 5,795,569; 5,879,673; and 5,989,537, incorporated in the patent specification by reference, disclose routes of administration of thrombopoietin, such as by intravenous or subcutaneous injection. See, e.g.,

U.S. Patent No. 5,879,673, lines 47-61. Thyroid hormone and thyrotropin are known in the art, and various drug forms are available as either an oral pill or as an injectable drug. The specification discloses the forms available and usual route of administration and dosage. See page 9, lines 6-20.

8. The time for effective treatment using the methods of my invention can easily be determined in an empirical manner. In general, a purpose of Phase II human clinical trials under the regulatory scheme adopted by the Food and Drug Administration is to determine effective dosing, including length of administration of the components to obtain the desired outcome. The conduct of clinical trials for this purpose is well known in the art, and is a routine and customary part of the development of any drug for use with humans.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

Date: July 24, 2001

  
George R. Schwartz